A case of Erdheim Chester disease with central nervous system involvement

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Abstract

Erdheim Chester disease (ECD) is a rare non-Langerhans cell histiocytosis, commonly involving the musculoskeletal system. Other tissue can also be involved, including the central nervous system with wide spectrum of clinical features, at times being nonspecific. This can cause diagnostic dilemmas with delay in diagnosis and initiation of therapy. Here we describe a 63-year-old man who had presented with ataxia and behavioral changes, bony pains, weight loss, and fatigue. His computed tomography (CT), 99Tc scintigraphy and histopathological features on bone biopsy were consistent with ECD. Thus, ECD should be considered as a differential diagnosis in patients presenting with bony pain and nonspecific features of multiorgan involvement.

Key Words

Erdheim Chester disease, histiocytosis, sclerotic bone

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Introduction

Erdheim Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis. The histiocytes are CD68 positive, CD1a negative, and lack Birbeck granules. Touton-like giant cells are commonly seen. ECD is characterized by bilateral symmetric long bone sclerosis. About half of the patients have extraskeletal manifestations, with about 40-50% having neurological features.[1-3] Here we describe a case of ECD with central nervous system (CNS) involvement, its clinical, imaging and histopathological features.

Case Report

A 63-year-old male presented with gradually progressive gait imbalance, upper limb incordination, behavioral changes (anger outbursts, emotional lability, and disinhibition), recent memory impairment, lower limb bony pains, weight loss, and fatigue since 1 year. He was evaluated elsewhere and treated symptomatically. On examination, he had generalized wasting, bilateral xanthelasma [Figure 1a], bony tenderness, emotional lability, perseveration, disinhibition, immediate and recent memory impairment, broken pursuit eye movements, up-gaze restriction, and bilateral cerebellar signs with gait ataxia. He was further evaluated with differentials of neurodegenerative, paraneoplastic, autoimmune, and toxic etiologies because of nonspecific clinical features with multisystem involvement. Blood counts and metabolic parameters were normal. Magnetic resonance imaging (MRI) brain showed diffuse hyperintensity in pons, medulla, and cerebellar peduncles bilaterally [Figure 1b]. Periventricular hyperintensities were also seen [Figure 1c]. A 99Tc bone scintigraphy showed increased uptake in bilateral humeral, femoral, tibial shafts, frontal, and maxillary bones [Figure 1d and e]. Whole body positron emission tomography (PET)-CT showed hyper metabolic diffuse cortical thickening of long bones with sclerosis in the metadiaphysis and sparing of epiphysis. Facial bones were also involved. A metabolically active focus was also seen in the brainstem [Figure 1f]. Small intraconal-enhancing nodules were seen along the extra-ocular muscles. Soft tissue thickening was seen along the aorta and its branches.

The clinical presentation and typical imaging finding (involvement of diaphysis and metaphysis, epiphysial sparing) were suggestive of ECD. Left humerus bone biopsy showed marrow infiltration with sheets of foamy histiocytes. Plasma cells and lymphocytes were also seen. Few of the trabeculae were sclerosed [Figure 2a and b]. On immunohistochemistry, histiocytes were negative for CD1a [Figure 2c]. Histopathological

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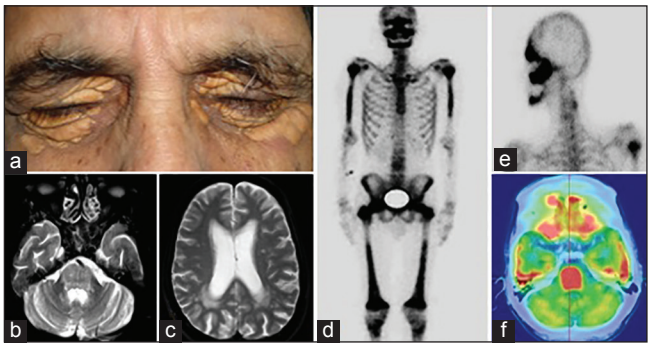

Figure 1: Photograph showing bilateral periorbital xanthelasma (a). MRI T2 axial images of the brain showing hyper intensity in the pons, middle cerebellar peduncles bilaterally (b) and cerebral subcortical/periventricular white matter (c). 99Tc bone scintigraphy showing bilaterally symmetric increased uptake in the metadiaphysial regions of humerus, femur, tibia, and also in the frontal and maxillary sinuses (d and e). PET-CT showing metabolically active focus in the pons (f). PET-CT = positron emission tomography computed tomography, MRI = magnetic resonance imaging

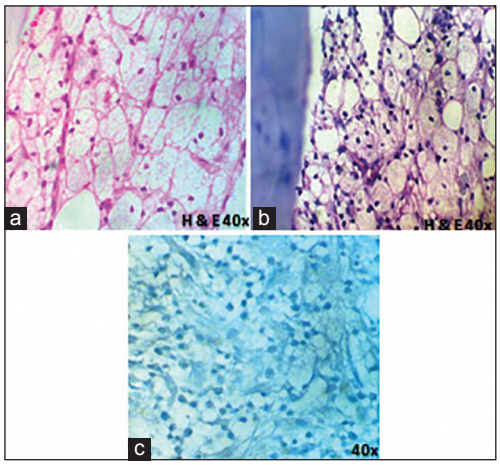

Figure 2: Histopathology images showing trabeculae of bone with infiltration of sheets of foamy histiocytes (a and b). Immunohistochemistry for CD1a showed negative immunostaining (c)

features (sclerotic bone with CD1a-negative foamy histiocytic infiltration) were of non-Langerhans histiocytosis. Overall clinical, imaging, and histopathological features were of ECD. He was started on weekly Interferon alpha. As there was no response after 2 months, he was initiated on methypredisolone and mycophenolate. At 4 months follow-up, he showed improvement in his symptoms.

Discussion

ECD was first described as "lipoid granulomatose" by Jakob Erdheim's student William Chester (1930). The term ECD was first coined by Jaffe HL (1972).[1,2,4] ECD predominantly involves the musculoskeletal system. In about half of the patients, retroperitoneum, cardiovascular system, lungs, orbits, and CNS are involved. Involvement of skin, testis, breast, and gastrointestinal system has also been infrequently reported.[1-3] In ECD, involvement of lymph nodes, liver, spleen, or axial skeleton is unusual, which is common in Langerhans cell histiocytosis (LCH).[2,3,5]

ECD is usually seen in fifth decade with slight male preponderance.[1-3] Based on the previous reports, median age at onset and diagnosis were 49 (range 4-87) years and 53 (range 4-87) years, respectively with diagnostic delay of 1 year (range 0-34).[2] Our patient was 63-year-old male, older than those described in literature and was symptomatic for one year before diagnosis.

Clinical presentation can vary from asymptomatic tissue infiltration, bony pains to multiorgan failure.[1,2] ECD presents commonly with skeletal symptoms, diabetes insipidus (DI), neurological, and constitutional symptoms.[2]

Bone involvement occurs in about 96% of the cases. ECD classically involves appendicular long bones, especially the distal femur, proximal tibia, and fibula, and less commonly the ulna, radius, and humerus. The most common presenting symptom is persistent bone pain (50% of patients) in lower limbs, especially around knees and ankles. The typical radiological features include bilateral symmetric medullary sclerosis and cortical thickening of the metadiaphysis with epiphysial sparing. Bone scans show intense bilateral, symmetric metadiaphysial tracer uptake. These radiological findings are considered pathognomonic of ECD. These findings are also seen in Gaucher's, Niemann-Pick's, and Fabry's disease. Partial epiphysial involvement and periostitis have also been reported. Involvement of the axial skeleton is rare.[1-3,5,6] Cranial bone involvement has been infrequently reported, but were seen in 80% of the cases analyzed by Aurelie *et al.* as osteosclerosis of the maxillary and sphenoid sinuses. This was seen as thickened bone on CT and hypointense signal on T1 and T2w MRI images.[7] In addition to sclerotic lesions, lytic lesions have also been described infrequently.[1,3] In our patient, both appendicular and facial bone involvement was seen.

CNS involvement is seen in about 40-50%, with half of these presenting with CNS symptoms at onset. The common locations include hypothalamo-pituitary axis, brain parenchyma, and meninges. CNS involvement usually manifests as DI and ataxia. DI is the initial manifestation in 22% due to nodular masses involving the infundibular stalk. Parenchymal lesions are common in the infratentorial region (brain stem, cerebellum, and middle cerebellar peduncles). These lesions can also be seen in the cerebral hemispheres and basal ganglia. These may appear hypointense on T2w MRI images with marked enhancement, or as symmetric hyperintensities on T2w MRI images. Meningeal involvement causes pachymeningeal thickening or circumscribed dural masses along the falx cerebri, tentorium, or sella. Cerebrovascular involvement can occur as peri-arterial infiltration. There is association between facial bones and orbital/meningeal involvement, indicating the diagnosis of ECD in appropriate clinical situations.[2,3,7-9]

Retroperitoneal involvement occurs in about two-third, as infiltration and fibrosis of the adrenal glands, kidneys, renal arteries, ureters, and surrounding anatomical spaces. One-third of the patients can have abdominal pain, ureteral obstruction with hydronephrosis/chronic renal failure, and renal artery

stenosis causing renovascular hypertension. On CT scans, this is seen as peri-renal infiltration extending through the fat of para-renal spaces (hairy kidney appearance).[1-3]

Cardiovascular system can be involved in ECD. Pericardial infiltration can cause pericarditis, effusion, and tamponade. Myocardial involvement can cause myocardial hypertrophy, infarction, cardiac failure, and valvular dysfunction, mainly aortic and mitral regurgitation. Conduction defects can also occur. Perivascular infiltration can cause periaortic fibrosis, appearing as coated aorta on CT scans. This can extend along the aortic branches causing arterial stenosis and subsequent ischemia.[2,3,10]

Lung involvement can cause interstitial infiltrates, pleural and interlobar septal thickening, and lung cysts, presenting as dry cough or dyspnea.[2,3,11]

Orbital lesions are usually seen as bilateral, intraconal enhancing masses sheathing the optic nerves or diffuse retro-ocular fat infiltration. These can be asymptomatic or cause exophthalmos and visual impairment.[3,7,9] Skin involvement can cause multifocal papulonodular lesions and xanthoma of the eyelids.[2,3]

Fever, night sweats, weight loss, and fatigue can also occur, with 20% presenting with these symptoms.[2,3]

Diagnosis is based on either histological or radiological findings. The typical histological findings include foamy histiocytic (CD68 positive and CD1a negative) infiltration in polymorphic granulomas with surrounding fibrosis or xanthogranulomatosis. The typical radiological findings include bilateral symmetric osteosclerosis and increased radiotracer uptake of the metadiaphysial regions of long bones.[1]

Our patient had presented with ataxia as the first symptom and then recruited features of frontal and temporal lobe involvement, bony pains, weight loss, and fatigue. These features were similar to those reported in literature.

PET-CT and bone scintigraphy in our patient showed metadiaphysial sclerosis with increased radiotracer uptake in long bones. Cardiac (soft tissue thickening along the aorta and its branches) and orbital (intraconal-enhancing nodules) involvement was seen in our patient. There were also features of CNS involvement (hyperintensities in pons, medulla, and cerebellar peduncles without enhancement on MRI). Bone biopsy had showed sclerotic bone with CD1a negative foamy histiocytic infiltration in our patient. Thus, our patient's clinical, imaging, and biopsy features were similar to those described in literature.

Recently BRAF-V600E point mutation has been described in LCH and ECD, suggesting the possibility of clonal proliferation. BRAF is a proto-oncogene and member of the serine-threonine kinase family. BRAF-V600E mutation results in activation of RAS-extracellular-signal-regulated kinase (ERK) pathway independent of RAS activation, leading to enhanced cell proliferation and survival. BRAF-V600E mutation is also seen in melanoma, hairy cell leukemia colorectal, and thyroid carcinoma. Haroche *et al.* reported positive BRAF-V600E mutation in 54% (13/24) of ECD and 38% (11/29) cases of LCH in 93 cases of histiocytosis. This mutation was not seen in other cases of histiocytosis. BRAF-V600E mutation in ECD has also been described by Blombery *et al*. Detection of BRAF-V600E mutation would help in understanding the pathogenesis and also has therapeutic implications, with BRAF inhibitor vemurafenib being studied in ECD.[12-14] BRAF-V600E mutation was not analyzed in our case.

Various modalities of therapy have been used in ECD. The first line therapy is interferon alfa. The second line therapies include anakinra, vemurafenib, imatinib, and cladarbine. Salvage therapies include vincristine, vinblastine, cyclophosphamide, methotrexate, and doxorubicin. Palliative therapies include prednisolone and bisphosphonates. Other modalities used include infliximab, mycophenolate, and stem cell transplantation.

Interferon alfa is the best therapeutic option with sustained disease stabilization. The duration of treatment is usually prolonged. The response to therapy depends on the site of disease, being better with skin involvement followed by CNS, pituitary, lungs, and heart involvement, which are more resistant to treatment. Heart and CNS disease requires high dose regimens. Treatment with interferon alfa is considered as independent predictor of survival.[3,15,16]

Infliximab in combination with steroids and methotrexate has shown benefit in cardiovascular disease. Cladarbine is considered as alternative first-line therapy, with reports showing partial to marked recovery. It is considered useful in patients with moderate-severe disease, especially of CNS, who are not suitable for vemurafenib or other second line modalities. Anakinra is a recombinant IL-1 receptor antagonist with antiinflammatory activity. It has shown to be effective in mild cases with disease stabilization. It has limited role in CNS and cardiovascular involvement. Vemurafenib is a BRAF inhibitor used in treatment of advanced melanoma. Haroche *et al.* reported about three ECD patients with BRAF V600E mutation having refractory multi-system disease treated with vemurafenib. There was clinical improvement and decrease in abnormal uptake on PET. Thus vemurafenib could be used in cases with BRAF V600E mutation having life-threatening multisystem disease.[3,12,14]

Steroids have transient/limited effect on the disease, being useful in cases of severe exophthalmos or in disease flare-up for transient control. Chemotherapy regimens have been used, but with only transient improvement. Chemotherapy is considered for disease refractory to first- and second-line therapies. Radiation therapy has been used as palliation therapy for osseous symptoms. Surgical resection has been used for mass effect on surrounding structures. Bisphosphonates have shown partial success by reducing bone pain. High-dose chemotherapy followed by autologous stem cell transplantation can be considered in patients with craniofacial/space-occupying brainstem lesions.[3,15] Based on review of literature, our patient was started on a weekly schedule of Interferon alpha. As there was no response after 2 months, he was initiated on pulse

methylprednisolone and mycophenolate. At 4 months he showed improvement in his symptoms.

About 60% of the patients die of their illness with a mean survival time of 19.2 months after diagnosis (range 0-120 months) as reported in earlier studies. With interferon alfa, therapy mortality decreased to 26%, with 5 year survival of 68%. The main causes of death are cardiac, pulmonary, or renal failure.[1,2,3,16]

Conclusion

A 63-year-old man had presented with ataxia, behavioral changes, bony pains, weight loss, and fatigue. His radiological and histopathological features were consistent with ECD. Thus, ECD should be considered as a differential diagnosis in patients presenting with bony pain and nonspecific/diverse features of multiorgan involvement. This also highlights diagnostic delay and the importance of musculoskeletal imaging in the diagnosis ECD.

Over the last 10 years, ECD cases have been reported with increasing number as it is has became better characterized. The increase in the number of case reports would provided basis for early diagnosis, further research into the etiology and therapy of ECD. ECD being multisystem disease, multidisciplinary approach would help in better patient care and management.

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